REMARKS

Claims 5-12 and 14-61 are currently pending in this application. Claims 1-4 and 13 are canceled. Claims 39-43 and 47-60 are withdrawn from consideration. Claims 37 and 38 are allowable. Claims 5-12, 14-36, 44-46, and 61 are under consideration. Applicants acknowledge that the Examiner has deemed claims 37 and 38 as allowable. Reconsideration and allowance of the application in light of the foregoing amendments and the following remarks are respectfully requested.

Claim Rejections Under 35 USC §112 Second Paragraph

The Examiner rejected claims 6-10, 12, 16-21, and 24 under 35 USC §112, second paragraph, contending that they are indefinite for the recitation of "IL-18 activity" and "neutralizing antibody". Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Not in acquiescence of the rejection but in order to expedite allowance of the claims, claims 5-10, 12, 16-21, and 24 have been amended to recite the exemplary neutralizing IL-18 activity of "inhibition of IFN-γ induction in KG1 cells". Support for the amendment can be found, for example, in Example 4, which describes the use of KG1 cells to determine the amount of IL-18 neutralization that occurred as a function of induced human IFN-gamma production.

In view of the foregoing amendments and remarks, Applicants respectfully request the removal of the rejection of claims 6-10, 12, 16-21, and 24 under 35 USC §112, second paragraph.

Claim Rejections Under 35 USC §112 First Paragraph

The Examiner rejected claims 23-27 and 32-35 under 35 USC §112, first paragraph, contending that the claims are not enabled because changes in the amino acid composition of the antibodies of the invention would require undue experimentation to test. Applicants traverse the rejections to the extent it is maintained over the claims as amended.

Not in acquiescence of the rejection but in order to expedite allowance of the claims, Applicants have amended the claims to require that any amino acid alterations do not inhibit IL-18 binding. Contrary to the Examiner's contention that the changes in amino acid composition would require undue experimentation to test, Applicants respectfully submit that such experimentation is routine and that

Applicants seek appropriate breadth in the claims, for example, so that competitors cannot simply alter an amino acid in order to design around a claim requiring a specific amino acid sequence. Applicants submit that in view of Examiner's concerns regarding the loss of affinity of an antibody due to minor alterations in sequence that claims 25-28 and 32-35 have been amended to require that the "substitution does not inhibit IL-18 binding".

In view of the foregoing amendments and remarks, Applicants respectfully request the removal of the rejection of claims 23-27 and 32-35 under 35 USC §112, first paragraph.

Claim Rejections Under 35 USC §103(a)

The Examiner rejected claims 4-12, 14-24, 44-46 and 61 under 35 USC §103(a) as being unpatentable over Kucherlapati et al. (US Patent No. 6,075,181) and Dinarello et al. (J. Leukoc. Biol. 1998; 63:658-664). Applicants traverse the rejections to the extent they are maintained over the claims as amended.

Applicants respectfully submit that claim 4 was canceled in the amendment filed on August 11, 2005 and therefore is not under consideration.

Applicants submit that the above-cited references, either singularly or in combination, do not teach, suggest, or motivate one skilled in the art, to make Applicants' human anti-IL-18 antibodies or methods of making the same as recited by the claims as amended.

Dinarello et al. disclose recombinant human IL-18 and identify IL-18 as a potential therapeutic target, and disclose possible "therapeutic options for specific blockade of IL-18", such as neutralizing anti-18 antibodies. Dinarello et al. do not teach, suggest or motivate one skilled in the art to generate fully human antibodies to human IL-18, nor does Dinarello set forth which epitopes such antibodies might be bound to or the dissociation constants and activity of the antibodies generated.

In particular, Dinarello et al. do not teach a human anti-IL-18 antibody that dissociates from human IL-18 with a k_{off} rate constant of $0.1s^{-1}$ or less, $1 \times 10^{-2}s^{-1}$ or less, $1 \times 10^{-3}s^{-1}$ or less, $1 \times 10^{-4}s^{-1}$ or less, $1 \times 10^{-5}s^{-1}$ or less, or $1 \times 10^{-6}s^{-1}$ or less as determined by surface plasmon resonance, as required by claims 5-10, 16-21, 44-46 and 61. Further, Dinarello et al. do not teach an anti-IL-18 antibody that inhibits human IL-18 activity of IFN-γ induction in KG1 cells with an IC_{50} of $1 \times 10^{-6}M$ or less, $1 \times 10^{-7}M$ or less,

1 x 10^{-8}M or less, 1 x 10^{-9}M or less, 1 x 10^{-10}M or less, or 1 x 10^{-11}M or less, as required by claims 5-10, 16-21, 44-46 and 61. Still further, Dinarello et al. do not teach a human IL-18 antibody that binds an epitope of human IL-18 comprising an amino acid sequence of either SEQ ID NO: 3 or 33 as required by claims 11-12, 14-15, 22-24, and 61.

Kucherlapati et al. disclose a method of generating fully human antibodies to antigens. Kucherlapati et al. do not disclose IL-18 as an antigen. Kucherlapati et al. do not teach, suggest or motivate one skilled in the art to generate fully human antibodies to human IL-18, nor does Kucherlapati set forth which epitopes such antibodies might be bound to or the dissociation constants and activity of the antibodies generated.

In particular, Kucherlapati et al. do not teach an anti-IL-18 antibody that dissociates from human IL-18 with a k_{off} rate constant of 0.1s^{-1}or less, 1 x $10^{-2}s^{-1}$or less, 1 x $10^{-3}s^{-1}$or less, 1 x $10^{-4}s^{-1}$or less, 1 x $10^{-5}s^{-1}$or less, or 1 x $10^{-6}s^{-1}$or less as determined by surface plasmon resonance, as required by claims 5-10, 16-21, 44-46 and 61. Further, Kucherlapati et al. do not teach an anti-IL-18 antibody that inhibits human IL-18 activity of IFN-γ induction in KG1 cells with an IC_{50} of 1 x 10^{-6}M or less, 1 x 10^{-7}M or less, 1 x 10^{-8}M or less, 1 x 10^{-9}M or less, 1 x 10^{-10}M or less, or 1 x 10^{-11}M or less, as required by claims 5-10, 16-21, 44-46 and 61. Still further, Kucherlapati et al. do not teach a human IL-18 antibody that binds an epitope of human IL-18 comprising an amino acid sequence of either SEQ ID NO: 3 or 33 as required by claims 11-12, 14-15, 22-24, and 61.

The Examiner asserts that one of ordinary skill in the art would have been reasonably expected to combine the teaching of Dinarello et al. with those of Kucherlapati et al. to produce Applicants' antibodies. Even though neither reference teaches explicitly a human monoclonal antibody to human IL-18, the Examiner asserts that it would be "instantly obvious" to one of ordinary skill in the art to combine the teaching of Dinarello et al. and Kucherlapati to arrive at Applicants' invention. However, without Applicants' disclosure, it is not obvious to one skilled in the art to make a leap from various therapeutic options as a clinical strategy to block IL-18 to one specific cure, namely a fully human anti-IL-18 antibody as described in the claims as amended with certain affinity and which binds to a particular epitope of IL-18.

The mere "[r]ecognition of the problem . . . does not render obvious the eventual solution. Recognition of a need does not render obvious the achievement that meets that need. There is an

important distinction between the general motivation to cure an uncured disease (for example, the disease of multiple forms of heart irregularity), and the motivation to create a particular cure." Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc. 381 F.3d 1371,1377 (2004).

Like Cardiac Pacemakers, the Dinerello et al disclosure of IL-18 as a potential target in inflammatory disease, at best, serves as recognition of a problem (i.e., IL-18 mediated disease), with no motivation to seek out, to investigate, or to explore the potential use of a fully human antibody to human IL-18 that has Applicants claimed characteristics as a solution. Kucherlapati et al. do not provide any motivation to create a particular cure or suggest IL-18 as an antigen (much less human IL-18). None of the cited art, singularly or in combination, provides any teaching, suggestion or motivation to arrive at Applicants' invention of a specific cure, a human anti-IL-18 antibody to human IL-18 as presently claimed.

In conclusion, Applicants assert that the Examiner fails to provide the requisite "*clear and particular showing*" of any suggestion or motivation to combine the cited references. The combination of the cited art is made by the Examiner, upon guidance, direction, and motivation to do so, by Applicants' present invention. Such hindsight reconstruction is impermissible as a basis for rejection under 35 USC §103. (see MPEP § 2142).

Because the cited art fails to satisfy the criteria necessary to establish or to sustain rejection of claims 5-12, 14-24, 44-46 and 61 as obvious under 35 USC §103(a). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 5-12, 14-24, 44-46 and 61 under 35 USC §103(a).

Conclusion

In view of the foregoing amendments and remarks, Applicants believe that the rejections set forth in the Office Action dated 26 October 2007 have been overcome and consequently that their application is in condition for allowance. Applicants, therefore, respectfully request reconsideration and removal of the rejections, and allowance of the claims as amended.

Respectfully submitted,

Diana M. Steel, D.Phil.
Registration No. 43,153
Attorney for Applicants
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
Telephone: (508) 688-8048
Telefax: (508) 688-8110